MEDICAL SCHOOL
UNIVERSITY OF MICHIGAN

Capstone for Impact Submission | GY2021

Project Title: Quantification of Retinal Nonperfusion and Neovascularization with Ultrawide-Field Fluorescein Angiography in Patients with Diabetes and Associated Characteristics of Advanced Disease

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If this project can be continued by another UMMS student, please include your contact information or any other details you would like to share here:

Summary (~250-500 words): Diabetic retinopathy (DR), an ophthalmic disease that occurs in patients with diabetes, is the leading cause of new cases of vision loss among U.S. working-aged adults between ages 20 to 74 years old, according to the US Centers for Disease Control and Prevention.[1] Currently the gold standard for evaluating DR disease progression is 7-field retinal fundus photography, but there are newer technologies now available such as ultra-widefield (UWF) imaging. It has been established that UWF images show more biomarkers known to have clinical relevance in DR, such as areas of nonperfusion (NP) and neovascularization (NV), and also demonstrates significantly higher severity than standard imaging, which could help elucidate which patients are at higher risk of severe DR at earlier stages, allowing for better management of such patients.[2-5] Though UWF imaging can provide important information regarding disease risk, there are currently no studies demonstrating how to objectively use such data to identify patients most in need for more aggressive treatment earlier. The purpose of this study was to quantify the surface areas of NP and NV in patients with diabetes using UWF fluorescein angiography (FA) and evaluate associations with potential DR risk factors. In addition, for this study, a threshold NP area associated with increased risk for proliferative disease was also calculated. Though in clinic, certain demographic risk factors may qualitatively seem associated with more severe DR due to clinical acumen, this study is attempting to identify objectively with quantitative methods which of these demographic risk factors truly are associated with more severe disease.

Methodology: We evaluated nine years of clinical data via retrospective chart review of adult patients diagnosed with diabetes that received a UWF FA obtained from Optos 200Tx or California machines at the University of Michigan Kellogg Eye Center (January 2009 and May 2018) after approval from the Institutional Review Board. Trained, masked graders segmented NP and NV regions for analysis. Eyes with severe media opacities, indistinguishable areas of NP or NV, or prior panretinal photocoagulation were excluded. Surface area was calculated with Optos research software and ITK-SNAP (Insight Registration and Segmentation Toolkit) for a nominal eye diameter of 24 mm. Multiple linear regression analysis was completed to determine significant associations.

Results: A total of 651 eyes from 363 participants were included: 76 eyes with no diabetic retinopathy (DR), 92 with mild non-proliferative diabetic retinopathy (NPDR), 144 with moderate NPDR, 101 with severe NPDR, 220 with proliferative diabetic retinopathy (PDR), and 18 with DR of unknown severity. Of 363 patients, 299 had type 2 diabetes (82.3%), 61 (16.8%) had type 1, and 3 had unknown type (0.8%). Most patients were male (205 patients, 56.5%) and white (247, 68%) or black (77, 21.2%). The mean age

was 59.4 ± 13.7 years. Male sex had a positive association with total NP (difference=15.72; 95% CI:4.83-26.61; P=.005); black race with total NV (difference=2.32; 95% CI:0.09-4.55; P=.04). Vitreous hemorrhage (VH), a marker of severe DR, was found in 18 eyes (2.8%) and had a significant positive association with total NP area (difference = 30.00, 95% CI: 5.26-54.75, P=.02). Other markers of severe DR, including presence of diabetic macular edema (374 eyes, 57.4%) and history of pars plana vitrectomy (35 eyes, 5.4%), had no significant associations with NP or NV. We identified a threshold total NP area of 77.48 mm^2 (95% CI: 54.24 – 92.66 mm^2), above which patients may have an increased risk of developing PDR (sensitivity of 59.5% and specificity of 73.6%).

Conclusion (~250-500 words): Our results indicate that the surface area of NP and NV can be quantified on UWF FA. In terms of demographic risk factors, male sex and black race were most associated with greater areas of total NP and NV, respectively. When considering characteristics generally associated with more severe DR, VH was most positively associated with a greater total area of NP in patients with diabetes. Eyes with at least 77.48 mm^2 of total nonperfusion are at increased risk of developing PDR. There are numerous studies and surveys describing the demographic characteristics of patients diagnosed with DR,[6-8] but they are limited by analyses that only compare presence or absence of disease and not incremental, quantifiable data like the areas of NP and NV at specific radii. With quantifiable data, correlations can be calculated, and the potential practicality of the associations may be better understood. One main limitation of this study was the unrepresentative breakdown of races, though it did have a larger percent of African Americans than previous studies.[2-5] Another limitation was the use of manual graders for segmentation due to potential variability and inaccuracy but should have been minimized with confirmation and training by the expert retinal specialist. Though images of poor quality were excluded, artifacts such as eyelashes still could have caused unintended variability. The quantification also assumed an eye diameter of 24 mm, which could have affected surface areas depending on actual axial lengths. Finally, a prospective study and not a cross-sectional retrospective study is warranted. The current results cannot be generalized due to these limitations. These biomarkers interpreted with demographic risk factors may help predict disease progression better; specifically, the associations between visually significant pathology, demographics, and biomarkers found in this study may suggest which populations are at higher risk for disease progression. More studies evaluating peripheral surface areas are necessary to validate these findings.

Sources:

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7. Centers for Disease Control and Prevention. National diabetes fact sheet: general information and national estimates on diabetes in the United States, 2007. http://www.cdc.gov/diabetes/pubs/factsheet07.htm. Accessed February 2, 2019

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Reflection/Impact Statement:

You may use the following questions to guide your reflection:

1. How did the process of conducting this research confront any limitations of your prior thinking?
2. Who could potentially benefit from this CFI project over different timescales and how?
3. What actions will you take afterwards to continue the momentum of this project, and maximise the likelihood of the identified benefits being achieved?
4. What advice would you give to another student completing their CFI?

I am grateful I had the opportunity to have completed a capstone for impact project on a topic that personally is very important to me. I wanted to study risk factors for severe diabetic retinopathy because my father has diabetes and he is monocular. Thus, taking great care of his eye is extremely important. However, he has several risk factors typically associated with worse DR, including age, male sex, and other underlying health conditions, and so I wanted to learn more about whether these risk factors predetermined him as having severe disease. The process of conducting this research made me realize that I was limited in my assumptions of what would cause more severe DR. I hypothesized that race and sex would significantly impact risk; however, I was surprised that age and diabetes type did not. I was limited in my thinking of who would need earlier and more aggressive treatment given what I had seen in clinic already. It also demonstrated the large disparities in research, especially in diabetes. Though the patient population I see for diabetic retinopathy is mostly African American or other people of color, the research has non-representative proportions of these races, which needs to be addressed.

I hope that this research will impact how we manage patients at risk for severe DR and help clinicians identify who would benefit most from earlier and more aggressive management. What is most concerning about DR is that it can remain asymptomatic, and so identifying such patients that will likely progress to more severe disease earlier is very important, especially since there might not be symptomatic markers to help with this decision. I also hope that this project will allow for more objective analysis of UWF FA, which could aid in telemedicine by providing low-resource hospitals with tools on how to quantifiably identify people at higher risk. Both potential impacts would likely take several years, but with the advancement of telemedicine, especially with COVID-19, this work could become even more impactful. Actions that I could take to continue momentum of this project is encouraging Optos to make the proprietary software of quantifying areas on UWF FA readily available on their machines. Also, there needs to be an automated method for segmenting pathologic areas, which will be difficult and require committed computer scientists and researchers. I hope that future students both interested in ophthalmology and computer science will continue this project.

For other students completing their CFI, I would encourage you to take advantage of the amazing resources that are available at the University of Michigan. Identify what you are passionate about – whether it is a question you have because of a close family member or a subject that has always piqued your interest – find mentors who are well-versed in that area of study (which will be easy at a place like Michigan!) and do not be afraid to reach for your goals. I was intimidated to work on this project when I was added on to the team, but I am happy that I went for it and worked hard to complete it. I am also so thankful I found amazing mentors in Dr. Yannis Paulus and other faculty at Kellogg. Without their help, this project would not have reached its fullest potential!